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EXAMINER	
WEHBE, ANNE MARIE SABRINA	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 11/08/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/701,022	ANDERSON ET AL.	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 September 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15-22 and 24-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-22 and 24-33* is/are rejected.

7)☒ Claim(s) *15-20,24-26,32 and 33* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This is a reissue application based on U.S. Patent No. 5,399,346 issued from U.S. application no. 08/220,175. Applicant's amendment and response filed on 9/2/05 has been entered. Claim 23 has been canceled and claims 30-33 have been added. Claims 15-22 and 24-33 are currently pending in this reissue application. Applicant's declaration under 37 CFR 1.132 and accompanying exhibits filed on 8/16/05 have also been entered. An action on the merits follows.

Those sections of Title 35, US code, not included in this action can be found in the previous office action.

35 U.S.C. 251

Since the applicant has amended the claims and added additional claims, the reissue oath/declaration filed on 5/6/04 is considered deficient. In accordance with 37 CFR 1.175(b)(1), a supplemental reissue oath/declaration under 37 CFR 1.175(b)(1) must be received before this reissue application can be allowed.

Claims 15-22 and 24-33 are rejected as being based upon a defective reissue oath/declaration under 35 U.S.C. 251. See 37 CFR 1.175. The nature of the defect is set forth above.

Receipt of an appropriate supplemental oath/declaration under 37 CFR 1.175(b)(1) will overcome this rejection under 35 U.S.C. 251. An example of acceptable language to be used in the supplemental oath/declaration is as follows:

> "Every error in the patent which was corrected in the present reissue application, and is not covered by a prior oath/declaration submitted in this application, arose without any deceptive intention on the part of the applicant."

Please note that any additional amendments submitted by applicants may also require a supplemental oath/declaration under 37 CFR 1.175(b)(1).

The rejection of previously pending claims 15-29 under 35 U.S.C. 251 and 37 CFR 1.658 as corresponding to the count lost in Interference No. 104,712, is **withdrawn over claims 21-23 and 27-31** in view of the cancellation of claim 23 and the Erratum to the judgment in Interference No. 104,712, see paper No. 92 of the interference proceedings- a copy of which was provided by applicants in their response received on 8/16/05, and **maintained over instant claims 15-20, 24-26, and 32-33**. Applicant's arguments have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection for reasons of record as discussed in detail below.

The applicant argues that the Erratum to the judgment in Interference No. 104,702 indicates that Anderson is not entitled to a patent containing claims 1-6, 8-11, 13, and 14 of Anderson's 5,399,346 patent, rather than claims 1-14 as the original judgment had stated. As such, the applicant argues while claims 7 and 12 were part of the count, no determination as to the priority of these claims was made and thus claims 7 and 12 were not deemed unpatentable. Since the applicant considers all of the pending claims in the instant application to be based on claims 7 and 12, the applicant argues that the instant claims do not correspond to the lost count.

In response, the examiner thanks the applicant for providing the copy of the Erratum to the Judgment in Interference No. 104,702. The original paper No. 92 in the Interference proceedings has been located by the examiner and placed in the appropriate location in the Interference file. Based on the corrected Judgment, the examiner agrees with the applicant that claims 21-22 and 27-31 correspond to patent claims 7 and 12 of the '346 patent and thus are not part of the lost count. However, the office finds that claims 15-20, 24-26, and 32-33 do not correspond to patent claims 7 and 12 and thus the rejection of record has been maintained over these claims. Specifically, claim 7 of the '346 patent was limited to a process for providing a human with a therapeutic protein comprising introducing human B lymphocytes into a human wherein the human B lymphocytes were treated *in vitro* to insert a DNA segment encoding a therapeutic protein. While instant claims 21 and 27-29 correspond to patent claim 7, claims 15-20, 24-26, and 32-33 do not as they are not limited to human B lymphocytes. Claim 12 of the '346 patent was limited to a process for providing a human with a therapeutic protein comprising introducing human cells into a human wherein the human cells were treated *in vitro* to insert a DNA segment encoding a therapeutic protein, wherein the therapeutic protein is an interleukin. While instant claims 22, 30 and 31 correspond to patent claim 12, claims 15-20, 24-26, and 32-33 as they are not limited to wherein the therapeutic protein is an interleukin. Please note that claim 10, which recited that the therapeutic protein was a cytokine, was "lost" as a result of the Judgment. Although the applicant has amended claim 15 to recite that the cytokine is " a cytokine other than TNF", Count 1 of the Interference corresponded to all cytokines. From the Erratum to the Judgment, the only cytokines not included in the lost count are interleukins. Therefore, claims 15-20, 24-26, and 32-33, which encompass cytokines which are not

interleukins, such as interferons, still correspond to the lost count. As such, the rejection of record stands.

The objection to previously pending claims 15-29 under 37 CFR 1.633 on the grounds of estoppel is **withdrawn over claims 21-23 and 27-31** in view of cancellation of claim 23 and the Erratum to the judgment in Interference No. 104,712, see paper No. 92 of the interference proceedings- a copy of which was provided by applicants in their response received on 8/16/05, and **maintained over instant claims 15-20, 24-26, and 32-33**. Applicant's arguments have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection for reasons of record as discussed in detail below.

The applicant argues that Anderson Preliminary Motion 5 (Paper No. 28) sought to designate claims 2-7 and portions of claims 8-14 of the '346 patent as not corresponding to the count, and that therefore the applicants did properly move under 37 CFR 1.633 and 1.634. As such, the applicant argues that the instant claims are not subject to estoppel.

In response, the Anderson Preliminary Motion 5 (Paper No. 28) sets forth their reasons for why they believed that claims 2-7 and portions of claim 8-14 did not correspond to the count. The reasons set forth by the Motion are based solely on the identity of the cells to be used in the methods. According to the motion, claims 2-7 are directed to various types of blood cells, and claims 8-14, to the extent that they depend on claims 2-7 in that they are multiple dependant claims, are also directed to blood cells. The motion argued that blood cells are separately patentable from the genus of human cells and particularly from the species of human epithelial cells or keratinocytes claimed by Morgan. Thus, the motion to separate claims 2-7 and portions

of claims 8-14 to the extent that they depend on claims 2-7 by Anderson was based solely on the species of the human cells claimed in claims 2-7, i.e. blood cells and more specifically B or T lymphocytes. Preliminary Motion 5 by Anderson did not seek to separate the use of specific cytokines other than TNF, such as interferons, from the count.

In view of the Erratum to the Judgment which excludes claim 7 which was directed to B lymphocytes and the Anderson Preliminary Motion 5, it is agreed that Anderson is not estopped from obtaining a patent on claims drawn to methods wherein the human cells are B lymphocytes. However, the office maintains that the applicant did not attempt to separate the subject matter of patent claims 10 and 12 from the count in view of their limitations to cytokines, TNF, or interleukins. The applicant failed to file a motion under 37 CFR 1.633(c)(1) seeking to add a separate count to methods wherein the therapeutic protein is a cytokine other than TNF or wherein the cytokine is an interferon or and interleukin. Further, while the Erratum to the Judgment excludes claim 12, wherein the therapeutic protein is an interleukin, the Judgment includes claim 10 directed to cytokines as a genus. Having lost the interference, Anderson et al. is therefore estopped from obtaining a patent containing claims to the methods reciting the genus of cytokines other than TNF or to the species of cytokines which are interferons. See 37 CFR 1.633 and MPEP 2363.03.

The rejection of claim 23 under 35 U.S.C. 251 as being based upon new matter added to the patent for which reissue is sought is withdrawn in view of the cancellation of claim 23.

Claim Rejections - 35 USC § 112

The rejection of previously pending claims 15-29 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, is **withdrawn over claims 19-20**, and **maintained in part over instant claims 15-18, 21-22 and 24-33**. Applicant's amendments, arguments, and the declaration under 37 CFR 1.132 by Dr. Rosenberg have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection for reasons of record as discussed in detail below. Please note that the rejection of claims 19-20 has been withdrawn in view of the Rosenberg declaration, see below for a detailed discussion.

Applicant's amendments to the claims to add the limitation that the cells are autologous overcomes the previous grounds of rejection regarding the administration of allogeneic cells.

In regards to the remaining grounds of rejection, the applicant argues that since claims 7 and 12 were found at one point by the office to be enabled, the instant rejection is improper. In response, each case is determined on its own merits. The instant case is a reissue application based on the '346 patent and the results of the Interference proceedings in which the '346 patent was involved. It is also noted that the instant claims are not identical to claims 7 and 12 of the '346 patent. Thus, the office properly examined the instant reissue application for compliance with all the relevant statutes concerning patentability.

The applicant further argues that since the claims are not directed to the treatment of disease that the specification is not required to provide guidance for disease treatment. In response, the claims as written clearly recite that the process as claimed is directed to providing a "therapeutically effective amount" of a therapeutic protein to a patient. The terms "therapeutic" and "therapeutically" are derived from the word therapy, which involves treatment. Thus, the

claims are clearly related to therapy and treatment. Further, the specification clearly sets forth that the purpose and use of the instant claimed processes is to provide sufficient levels of a protein to effectively treat various diseases such as ADA and cancer. As such, based on the limitations of the claims as written and based on the guidance provided by the specification, it is clear that the instant claims relate to the treatment of disease by providing "therapeutically effective amounts" of a therapeutic protein to a human.

The applicant then sets forth the factors to be considered in determining whether a disclosure is enabling according to *In re Wands*, and further cites United States v. Telectronics, Inc. for stating that, " [a] patent may be enabling even though some experimentation is necessary; however, the amount of experimentation must not be unduly extensive". The applicant follows these statements with their analysis of the guidance provided by the specification, including the teachings of the working examples, and concludes that the specification as filed provides an enabling disclosure for the invention as claimed.

In response, the previous office action analyzed the specification in direct accordance to the factors outlined in *In re Wands*, namely 1) the nature of the invention, 2) the state of the prior art, 3) the predictability of the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the quantity of experimentation necessary, 7) the relative skill of the skilled artisan, and 8) the breadth of the claims, and presented detailed scientific reasons supported by publications from the prior art for the finding of a lack of enablement for the scope of the instant methods. It is also noted that case law including the Marzocchi decision sanctions both the use of sound scientific reasoning and printed publications to support a holding of non-enablement (see *In re Marzocchi* 169 USPQ 367, and *Ex parte Sudilovsky* 21 USPQ2d

1702). Further, the unpredictability of a particular art area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See *Ex parte Singh*, 17 USPQ2d 1714 (BPAI 1991). 35 U.S.C. 112 also requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art. *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970). The previous office action further provided a detailed analysis of the guidance provided by the specification, including the working examples, and explained why these teachings in combination with the state of the art of gene therapy at the time of filing do not provide an enabling disclosure for the breadth of the claimed invention without undue experimentation.

In particular, the previous office action stated that although the specification provides a broad general description of the cells to be transfected, therapeutic genes to be expressed, and diseases to be treated, the majority of the specification is specifically directed to the treatment of either ADA deficiency or cancer by administering autologous human T lymphocytes obtained from peripheral blood or autologous human tumor-infiltrating lymphocytes (TIL), primarily composed of T lymphocytes, which have been transfected *ex vivo* with recombinant retroviruses which encode and express either ADA or TNF respectively. The working examples also disclose protocols for treating cancer by administering autologous tumor cells transduced *ex vivo* with recombinant retroviruses encoding TNF or IL-2, followed by the administration of TIL and recombinant IL-2 protein. Although the working examples describe protocols for preparing transduced autologous human TIL or tumor cells, the specification only provides actual data for human peripheral blood T-lymphocytes transduced with retrovirus encoding ADA. Working example 5 provides data for the treatment of a single patient with transduced autologous T-

lymphocytes expressing ADA. Figures 4 and 5 demonstrate that following multiple infusions of transduced T -lymphocytes, in dosages varying from 0.6X10-9 cells to 18X10-9 cells, the patient had detectable levels of transduced T cells in the blood secreting detectable levels of ADA. However, it is noted that the specification does not indicate whether the level of ADA expression observed correlated with any particular therapeutic effect on the patient. In regards to the other protocols set forth in the specification, the examples do not provide any specific guidance on the dosages of TIL or tumor cells expressing any particular level of TNF or IL-2 which correlates with a therapeutic effect on any type of cancer. In addition, the specification fails to provide any specific guidance for making and using transducing B lymphocytes, or provide any guidance or evidence regarding the treatment of any disease by administering transduced B lymphocytes expressing a therapeutic protein.

Further, the previous office action set forth the state of the art of gene therapy at the time of filing. At the time of filing, circa 1991, the field of gene therapy was in its infancy. The skilled artisan at the time of filing did not consider the therapeutic transplantation of transfected/ transduced human cells into human patients as either routine or predictable. In 1987, the Los Angeles Times reported that most researchers skilled in the field of gene therapy believed that successful gene therapy in humans was still years in the future (Barry Siegel, Los Angeles Times, Sunday edition, December 13, 1987, "GENES: Debate over Human Experimentation: Part I"). In the same article, Richard Mulligan stated that as of 1987, "[t]here is absolutely no shred of evidence that it will work" (ibid, page 37). Stuart Orkin agreed stating, "[g]ene therapy is a stunt...[w]e are just plodding along right now. We don't know why or what works" (Los Angeles Times, Monday edition, December 14, 1987, "GENES: Debate over Human

Experimentation: Part II"). In 1989, Buderi reported that on progress in gene therapy, "..scientists discovered that gene therapy isn't so simple after all. Even finding a means of inserting a gene into a person-most approaches use a stripped-down retrovirus to deliver the new gene-has proven to be a quagmire of unforeseen problems. And if they solve these problems, scientists face the monumental task of inducing the inserted gene to produce the right amount of enzyme (or other protein missing in each genetic disease) at the right time" (Robert Buderi, The Scientist, 1989, Vol. 3, No. 2, pages 1-3, see page 2). Summing up the opinions of the skilled researcher in 1989, Boderi stated, "[t]hese researchers have learned from hard experience that the underlying science necessary for successful gene therapy is still in its infancy" (ibid, page 3). Friedmann, also reviewing the progress of human gene therapy in 1989, found that many problems remain to be solved before successful human clinical application could be expected, including problems with the efficiency of gene delivery and expression, problems with stable expression, and problems identifying, culturing, genetically modifying, and transplanting appropriate cell types to treat different diseases (Friedmann, Science, June 16, 1989, Vol. 244, Issue 4910, page 1275-1281). Regarding the use of retroviruses to transfer and express genes in cells, Friedmann states that integrated retroviral sequences show high-frequency structural and functional instability, and that, "..vector design, the nature of the target cell, the presence or absence of selection pressure, and the nature of the expressed genes can contribute to vector instability by mechanisms still not fully understood" (Friedmann, page 1276). Friedmann also specifically teaches that the expression of retrovirally transduced genes in bone marrow cells and other less differentiated cells is transient and unstable (Friedmann, page 1278). In addition, Friedmann identifies specific problems with identifying and genetically modifying appropriate

cells for particular genetic diseases. Regarding genetic diseases of the CNS, Friedmann states, "[e]xperience with [Lesch-Nyhan disease] and others such as Alzheimer's and Parkinson's disease has made it clear that genetic approaches to the dysfunctioning mammalian CNS are not entirely straightforward. Useful models for genetic approaches to therapy of CNS disorders are difficult to identify for the following reason: (i) little is known about normal or abnormal CNS function, (ii) the organ and many of its cells are inaccessible both physically and physiologically, and (iii) most disorders affecting CNS function are likely to be multigenic and multifactorial. Furthermore, most of the presumed target cells for CNS disorders, neurons, are postmitotic and therefore refractory to infection with retroviral vectors" (Friedmann, page 1278). In 1990, Culliton reported on the approval process for two gene therapy protocols in humans, and in particular one for treating malignant melanoma by administering autologous TIL retrovirally transduced to express TNF. Culliton quotes Rosenberg, one of the instant inventors, as saying that, "So far, gene therapy has been an abstract idea, and it is easy to think about the risks when there are no evident benefits. The climate will change if the experiments work." (Culliton, Science, August 31, 1990, Vol. 249, Issue 4972, pages 974-976, see page 976). Further, in 1992, reviewing progress in human gene therapy, Roemer and Friedmann conclude that while progress has been made toward the genetic correction of disease, " ..the permanent correction of a phenotype based on a genetic defect in humans by means of gene transfer and expression has so far not been achieved" (Roemer and Friedmann, Eur. J. Biochem., 1992, Vol. 208, 211-225, see page 223). Roemer and Friedmann also state in regards to human clinical trials underway as of 1992, that, "[t]hese and other experiments will certainly provide information in the near future about whether our current technical skills are sufficient to permit long-term correction of genetic

disorders in human patients. Whatever the conclusion of these studies may be, we are optimistic that further progress in manipulating the human genome will eventually lead to means of overcoming many human maladies" (ibid, page 223). Thus, it is clear that up to the time of filing in December of 1991, the skilled artisan did not consider gene therapy of humans as predictable. Furthermore, even after the time of filing, the unpredictability of human gene therapy continued to be recognized by the skilled artisan. In 1993, Mulligan reviewed the basic technical hurdles to successful gene therapy in humans and concluded that, "[t]he transplantation of transduced cells remains the most serious technical obstacle to the successful development of ex vivo gene therapies.", and that, " [t]he major technical limitation of current methods for delivering genes in vivo is that the persistence of the transferred genes is transient, and therefore gene expression is transient as well" (Mulligan, Science, May 14 1993, Vol. 260, Issue 5110, pages 926-932, see page 931). Mulligan also states that, " ..basic science issues underlie many of the problems that need to be overcome in order for gene therapy to succeed" (ibid, page 931).

From the above discussion of the state of the art of gene therapy, it is clear that several key problems with *ex vivo* human gene therapy were well known to the skilled artisan at the time of filing. In particular, the art cited above identified problems with the instability of the commonly used retroviral vectors in cells, difficulties in successfully transducing less differentiated and non-dividing cells, problems with transient gene expression, and problems associated with the persistence of the transduced cells once they are transplanted into the host. The specification fails to provide sufficient guidance to overcome these significant problems such that the skilled artisan would predict success in expressing therapeutic levels of a protein following the disclosed methods of *ex vivo* gene therapy. Regarding the ability to successfully

transduce various cell types, while the specification broadly discloses the transduction of any primary human cell, including bone marrow stem cells, the specification only provides specific guidance for transducing human T lymphocytes present in peripheral blood or TIL. It is noted that while the specification proposes a protocol to transduce human tumor cells, no actual data is provided. In view of the physiological differences between cells types, and the teachings in the prior art that many cell types and particularly bone marrow and non-dividing cells are refractory to retroviral transduction, see above, the skilled artisan would not be able to extrapolate the applicant's results with T lymphocytes to other types of cells including tumor cells, bone marrow cells, or B lymphocytes. Further, as discussed above, while the applicant's working examples do demonstrate that multiple infusions of retrovirally transduced T -lymphocytes expressing ADA, in dosages varying from 0.6X10-9 cells to 18X10-9 cells, resulted in detectable levels of transduced T cells in the blood secreting detectable levels of ADA, there is indication that this level of transduced T cells expressing this amount of ADA is in fact a therapeutic amount, or is capable of successfully treating ADA deficiency. In addition, there is no evidence presented in the specification that other types of cells transduced with the same retrovirus encoding ADA would be capable of persisting in the human host and expressing the same level of ADA as the transduced T lymphocytes. In regards to the expression of other genes, and particularly cytokines other than TNF, such as interleukins or interferons, the specification provides no specific guidance as to the level of expression of any of these proteins which correlates with a therapeutic effect on any disease or condition, or provide any evidence that any type of human cell transduced with the disclosed retroviral vectors, or any other type of vector, would be capable of stably expressing such a therapeutic level of each protein once transplanted into a human host.

Therefore, in view of the undeveloped state of the art of human gene therapy at the time of filing, the recognition in the prior art of the high level of unpredictability of successful human gene therapy, the art recognized problems associated with achieving the expression of therapeutic levels of protein expressed from transduced cells *in vivo*, the lack of guidance provided by the specification for overcoming the art recognized problems, the lack of correlation between applicant's single working example which demonstrates detectable expression of a single gene from transduced autologous T lymphocytes and the therapeutic expression of any type of therapeutic protein including interleukins and interferons from any type of transduced human cell, including B lymphocytes, and the breadth of the claims, the previous office action concluded that it would have required undue experimentation for the skilled artisan to practice the processes for providing a human with a therapeutically effective amount of a therapeutic protein as claimed.

In regards to the point made by the Office that the specification does not provide sufficient guidance for using transduced B-lymphocytes in the instant claimed processes, the applicant argues that it appears that the Office is improperly requiring that the specification teach how to carry out every possible embodiment of the present invention, citing *In re Howarth* and *In re Gay* . In response, it is noted that the use of transfected/transduced B lymphocytes is a specific limitation of instant claims 21, and 27-29. Thus, the question of whether the specification provides sufficient guidance for practicing the claimed processes with B lymphocytes is clearly integral to the enablement of at least claims 21 and 27-29. The use of B lymphocytes for these claims is not just a "possible" embodiment for these claims, but rather is an essential element. Therefore, applicant's argument is not persuasive.

The applicant further argues that MPEP 2164.05 allows an applicant to provide a declaration after the filing date which demonstrates that the claimed invention works and that two such declarations have been provided with the instant response, the Rosenberg declaration under 37 CFR 1.132 and a copy of the Anderson declaration under 37 CFR 1.132 previously filed during prosecution of the 07/904,662 application. According to the applicants, these declarations provide evidence that the protocols disclosed in the specification served as the basis for other gene therapy clinical protocols using different genes and different cells and that therefore, the protocols disclosed in the specification sufficiently enable the breadth of the claims as written.

In response, it is first noted that in addition to stating that factual declarations may be submitted by the applicant to demonstrate enablement, MPEP 2164.05 also states that the weight to give a declaration or affidavit will depend upon the amount of factual evidence the declaration or affidavit contains to support the conclusion of enablement. *In re Buchner,* 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *cf. In re Alton, 76* F.3d 1168, 1174, 37 USPQ2d 1578, 1583 (Fed. Cir. 1996). To overcome a *prima facie* case of lack of enablement, applicant must demonstrate by argument and/or evidence that the disclosure, as filed, would have enabled the claimed invention for one skilled in the art at the time of filing. This does not preclude applicant from providing a declaration after the filing date which demonstrates that the claimed invention works. However, the examiner should carefully compare the steps, materials, and conditions used in the experiments of the declaration with those disclosed in the application to make sure that they are commensurate in scope; i.e., that the experiments used the guidance in the specification as filed and what was well known to one of skill in the art. Such a showing also

must be commensurate with the scope of the claimed invention, i.e., must bear a reasonable correlation to the scope of the claimed invention. MPEP 2164.05.

The evidence provided by each of the declarations has been respectfully considered by the examiner, but has not been found persuasive in overcoming the instant grounds of rejection. Turning first to the Anderson declaration, the Anderson declaration provides various tables and graphs concerning the increasing number of gene therapy protocols approved by the RAC, and states that since some of these protocols were based on the protocols disclosed by applicants, the approval for clinical trials demonstrates that the skilled artisan believed there was a reasonable expectation of efficacy. However, the declaration, while listing 18 different gene candidates used in clinical trials from the time of filing to 1993, does not identify the actual protocols by which any of these genes were introduced in the patients. The declaration states that various methods were used including *ex vivo* and *in vivo* transduction of cells, but does not provide any specifics. Further, while the declaration provides a graph showing that an increasing number of patients have received some form of therapy, the declaration does not provide any factual evidence as to the patient responses to the therapy, i.e. was gene expression in the patient observed and did that gene expression correlate with any actual therapeutic effect on the patient. Therefore, the relevance and significance of these post-filing clinical protocols cannot be determined from the Anderson declaration, nor can it be determined whether any of the protocols and results obtained in these clinical trials are commensurate in scope with any of the instant claims.

In regards to the Rosenberg declaration, the declaration states that the TNF protocol described in example 4 of the specification was used in at least one human patient. Dr. Rosenberg states, without providing any of the actual data, that the disclosed TNF protocol using

transduced TIL successfully provided a patient with a therapeutically effective amount of TNF. The Rosenberg declaration also states, again without providing any actual data, that the same protocol was used to deliver therapeutically effective amounts of IL-2 or a T-cell receptor to a patient. Other statements in the Rosenberg declaration include the disclosure of various clinical trials using cytokines such as IL-15, IL-21, or IFN-gamma in protocols based on the TNF protocol, and another trial which uses CD34+ stem cells. However, in regards to any of these trials, the declaration does not provide any actual data or report that gene expression in the patient observed that correlated with any actual therapeutic effect on the patient. Furthermore, while the Rosenberg declaration does provide statements that the administration of TIL transduced with TNF, IL-2, or a T-cell receptor was successful in providing therapeutically effective amounts of these proteins, these examples are not commensurate in scope with the claims as written. The claims as written are directed to two distinct methods: 1) a process for providing a human with a therapeutically effective amount of a therapeutic protein which is a cytokine other than TNF comprising introducing autologous human cells into a human, wherein the human cells have been treated *in vitro* to insert a DNA segment encoding the cytokine other than TNF; and 2) a process for providing a human with a therapeutically effective amount of a therapeutic protein comprising introducing autologous human B-lymphocytes into a human, wherein said human B-lymphocytes have been treated *in vitro* to insert a DNA segment encoding the therapeutic protein. The declaration has provided statements as to the effectiveness of TIL transduced with TNF, IL-2, or a T cell receptor. While, as the declaration states, TIL may contain more than T lymphocytes, neither the specification nor declaration demonstrate that TIL contain B lymphocytes or that it is B lymphocytes transduced with one of these genes that is in

fact responsible for the therapeutic effect on the patient. Further, the specification clearly considers the transduction of TIL as a means for producing transduced T lymphocytes, as evidenced by the fact that the protocol disclosed in example 4 of the specification is entitled, "GENE MODIFIED T-CELL CLINICAL PROTOCOL". In addition, at least one of the genes listed, the T cell receptor, is a membrane bound protein exclusive expressed in T cells, whose activity is dependent on various intracellular signaling proteins which are also specific for T cells. As such, the skilled artisan would have no expectation that expression of a T cell receptor in other cells types, such as epithelial cells, or even B lymphocytes, would be therapeutically effective. Therefore, analyzing the evidence provided by the declaration as a whole, the declaration, while providing statements that transduced TIL can be used to express therapeutically effective amounts of a cytokine or a T cell receptor, does not provide any evidence for the use of other types of cells. Thus, while the declaratory evidence is considered commensurate in scope with claims 19-20, and thus these claims have been withdrawn from this rejection, the evidence is not commensurate in scope with claims 15-18, 21-22 and 24-33.

The instant response also included two post-filing references by Blaese et al. and Onodera et al., which disclose the results of clinical trials conducted using T lymphocytes transduced with the ADA gene for the treatment of SCID. While these references provide data for the expression of therapeutically effective amounts of ADA in these patients using the transduced T lymphocytes, this evidence is not correlative to any of the instant claims. Claims 15-18, 21-22 and 24-33 are directed to either the administration of the any type of human cell transfected/transduced with gene encoding a cytokine other than TNF, or the administration of B lymphocytes encoding any therapeutic gene. As ADA is not a cytokine, the relevance of this data

to these claims is unclear. In regards to claims directed to the use of B lymphocytes, the references provided teach that the choice of cells for ADA therapy is important. Specifically, Blaese et al. teaches that while ADA deficiency is characterized by defective T and B cell function in donor bone marrow transplantation, the only cells detected in patients "cured" by the treatment are T cells, the other cells remained ADA-deficient (Blaese et al., page 475). Thus, Blaese et al. teaches that correcting T cells is essential to treating ADA- SCID. Thus, these references provide no suggestion or expectation of success that an cell other than a T lymphocyte could be used in the disclosed protocols.

Finally, the applicant argues that because of the number of clinical trials approved by the RAC, the office is in error in finding that a high degree of unpredictability regarding gene therapy existed at the time of filing. This is not agreed, as reiterated above, the prior office action cited numerous references which establish that both before and after the time of filing, and despite the approval of various clinical trials, that the skilled artisan did believe prior to 1991 and continued to believe after 1991 and at least up until 1993 that the expression of therapeutically effective amounts of genes in humans was unpredictable, see the LA Times articles, Buderi, Friedmann, Culliton, Roemer, and Mulligan, all cited above and in the previous office action. In addition, it is noted that the applicant's themselves argued that "overwhelming skepticism" existed in the prior art at the time of filing concerning the applicant's proposed gene therapy protocols, see for instance papers 24 and 28 of the 104,712 Interference proceedings. Thus, applicant's arguments are not found persuasive in overcoming the rejection of record as supported by numerous publications from the prior art.

Thus, having carefully considered all of applicant's arguments, evidence, and claim amendments, the office does not find that the evidence as a whole overcomes the rejection of record over claims 15-18, 21-22 and 24-33.

Claim Objections

Claim 25, as amended, is newly objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim should refer to other claims in the alternative only. See MPEP § 608.01(n). Appropriate correction is required.

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. The examiner can be reached Monday- Friday from 10:30-7:00 EST. If the examiner is not available, the examiner's supervisor, Dave Nguyen, can be reached at (571) 272-0731. For all official communications, **the new technology center fax number is (571) 273-8300**. Please note that all official communications and responses sent by fax must be directed to the technology center fax number. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737. For any inquiry of a general nature, please call (571) 272-0547.

The applicant can also consult the USPTO's Patent Application Information Retrieval system (PAIR) on the internet for patent application status and history information, and for electronic images of applications. For questions or problems related to PAIR, please call the USPTO Patent Electronic Business Center (Patent EBC) toll free at 1-866-217-9197. Representatives are available daily from 6am to midnight (EST). When calling please have your application serial number or patent number available. For all other customer support, please call the USPTO call center (UCC) at 1-800-786-9199.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER